



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,645	08/01/2003	Linda B. Couto	51271/35:1	5318
24536	7590	07/19/2006		
GENZYME CORPORATION LEGAL DEPARTMENT 15 PLEASANT ST CONNECTOR FRAMINGHAM, MA 01701-9322			EXAMINER WHITEMAN, BRIAN A	
			ART UNIT 1635	PAPER NUMBER

DATE MAILED: 07/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,645	COUTO ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) 4 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 5-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 June 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>10/14/03;10/2/03</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> . |

DETAILED ACTION

Non-Final Rejection

Claims 1-11 are pending.

The sequence listing filed on 6/9/06 is acknowledged. However, there is a problem with the CRF. See attached Notice to Comply.

Election/Restrictions

Applicant's election without traverse of species TTR gene promoter in the reply filed on 6/9/06 is acknowledged.

Claim 4 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/9/06.

Priority

The status of parent applications (09/470,618, 09/364,862) needs updated.

Drawings

The drawings were received on 6/9/06. These drawings are accepted.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Art Unit: 1635

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the limitation "said tissue specific promoter" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The limitation “pharmaceutical composition” in instant claim 1 and claims dependent therefrom does not have patentable weight over the product taught in the prior art. See MPEP 2111.02.

Claims 1-3, 6, and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Snyder et al. (US 2002/0155580, cited on an IDS). Snyder teaches a virus particle comprising a recombinant AAV vector comprising a promoter operably linked to a polynucleotide encoding a polypeptide comprising the factor VIII 90kD heavy and light chain with the B-domain deleted (pages 5-12). Snyder teaches that the AAV lacks AAV rep and cap gene (pages 10-11). The

Art Unit: 1635

promoter in the vector can be tissue specific for the liver. Snyder further teaches preparing the virus particle in a pharmaceutical excipient (page 7).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Snyder et al. (US 2002/0155580, cited on an IDS) taken with Simonet (US Patent No. 6,268,212, cited on an IDS). Snyder teaches a virus particle comprising a recombinant AAV vector comprising a promoter operably linked to a polynucleotide encoding a polypeptide comprising the factor VIII 90kD heavy and light chain with the B-domain deleted (pages 5-12). Snyder teaches that the promoter can be tissue specific for the liver (page 4). Snyder further teaches that one of ordinary skill in the art will appreciate that a tissue-specific promoter for use in the AAV vector may be selected from any of the known liver-specific promoters (page 4). However, Snyder does not specifically teach a composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding a B-domain deleted human Factor VIII protein operably linked to a liver specific promoter, wherein the liver-specific promoter is the transthyretin (TTR) gene promoter.

However, at the time the invention was made, tissue specific promoter, specifically liver-specific promoters (e.g. TTR) were well known in the art for use in enhancing liver expression of a transgene using a vector as exemplified by Simonet. Simonet teaches several liver-specific promoters (e.g. TTR) that could be used in producing a vector comprising a transgene operably linked to a liver-specific promoter (column 3, line 64-column 4, line 12 and abstract).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention made to combine the teaching of Snyder and Simonet to make a composition comprising a recombinant AAV comprising a nucleotide sequence encoding a B-domain deleted human Factor VIII protein operably linked to a liver specific promoter TTR. One of ordinary skill in the art would have motivated to make the claimed composition because factor VIII is

Art Unit: 1635

expressed in the liver and the promoter TTR used to increase gene expression of a vector in the liver.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 6, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Snyder et al. (US 2002/0155580) taken with Almstedt et al. (WO 91/09122, cited on an IDS). Snyder teaches a virus particle comprising a recombinant AAV vector comprising a promoter operably linked to a polynucleotide encoding a polypeptide comprising the factor VIII 90kD heavy and light chain with B-domain deleted (pages 5-12). Snyder teaches that in order to improve expression efficiency of Factor VIII, the Factor VIII cDNA was modified lacking most of the B domain (page 2). However, Snyder does not specifically teach a composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding a functional Factor VIII, wherein the nucleotide sequence encodes a heavy and a light chain of Factor VIII with the B domain deleted, and wherein said light chain and heavy chain of Factor VIII are operably linked to a junction having SEQ ID NO: 15.

However, at the time the invention was made, a recombinant factor VIII protein comprising a first DNA segment coding for the 90kDa chain and a second DNA segment coding for the 80kDa chain of human factor VIII, wherein the segments were interconnected by a linker DNA segment coding for a linker peptide of 4 to about 100 amino acid residues (having SEQ ID NO: 15 of the instant claims) was well known in the art as exemplified by Almstedt (abstract). Almstedt further teaches that the DNA sequence can be expressed in recombinant expression

Art Unit: 1635

vectors (abstract). In addition, Almstedt teaches that the smallest active form (one heavy chain and one light chain) with a molecular weight of 170kDa could be activated by thrombin to the same extent as the high molecular weight forms and there was an indication that that smaller form has a 50% longer survival time compared to the higher molecular form (page 4).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention made to combine the teaching of Snyder and Almstedt to make a composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding a B-domain deleted Factor VIII protein, and wherein said nucleotide sequence further encodes a junction (SEQ ID NO: 15) that operably links said heavy and light chain of Factor VIII. One of ordinary skill in the art would have motivated to make the composition because Almstedt teaches that the smaller form of Factor VIII comprising both chains has a 50% longer *in vivo* survival time compared to the higher molecular forms of Factor VIII.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 and 6-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 6,200,560. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claim from the instant application and the claims from '560 are both directed a recombinant adeno-associated virus comprising a nucleotide sequence encoding a Factor VIII protein operably linked to a promoter.

The claims from '560 do not specifically recite a nucleotide sequence encoding a Factor VIII lacking at least a portion of the B domain. However, in view of the definition of Factor VIII in the specification of '560, the claims of '560 read on the instant claim because the specification teaches that Factor VIII is lacking a B domain (Figure 3). See MPEP 804 which recites that those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent (*In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970)).

Claims 1-3 and 6-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 6,221,349. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claim from the instant application and the claims from '349 are both directed to a

Art Unit: 1635

recombinant adeno-associated virus comprising a nucleotide sequence encoding a Factor VIII protein operably linked to a promoter.

The claims from '349 do not specifically recite a nucleotide sequence encoding a Factor VIII lacking at least a portion of the B domain. However, in view of the definition of Factor VIII in the specification of '349, the claims of '349 read on the instant claim because the specification teaches that Factor VIII is lacking a B domain (Figure 3). See MPEP 804 which recites that those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent (In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970)).

Claims 1-3 and 6-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 10/293,400. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims embrace a pharmaceutical composition comprising recombinant adeno-associated virus virions comprising a nucleotide sequence encoding a Factor VIII protein lacking at least a portion of the B domain and the nucleotide sequence operably linked to expression control elements. Both set of claims recite using SEQ ID NO: 13 and 14 (which are 100% identical to SEQ ID NO: 13 and 14 of the instant claims).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, SPE – Art Unit 1635, can be reached at (571) 272-4517.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

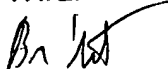
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
Patent Examiner, Group 1635

BRIAN WHITEMAN
PATENT EXAMINER



Notice to Comply	Application No. 10/632,645	Applicant(s) COUTO et al.	
	Examiner B. Whiteman	Art Unit 1635	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☒ 7. Other: See Raw sequence listing error report.

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the specification.**
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510

For CRF Submission Help, call (571) 272-2501/2583.

PatentIn Software Program Support

Technical Assistance.....703-287-0200

To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

B. Whiteman

STIC Biotechnology Systems Branch

RAW SEQUENCE LISTING **ERROR REPORT**

The Biotechnology Systems Branch of the Scientific and Technical Information Center (STIC) detected errors when processing the following computer readable form:

Application Serial Number: 10/632,645A
Source: FW/6
Date Processed by STIC: 6/14/06

THE ATTACHED PRINTOUT EXPLAINS DETECTED ERRORS.

PLEASE FORWARD THIS INFORMATION TO THE APPLICANT BY EITHER:

- 1) INCLUDING A COPY OF THIS PRINTOUT IN YOUR NEXT COMMUNICATION TO THE APPLICANT, WITH A NOTICE TO COMPLY or,
- 2) TELEPHONING APPLICANT AND FAXING A COPY OF THIS PRINTOUT, WITH A NOTICE TO COMPLY

FOR CRF SUBMISSION AND PATENTIN SOFTWARE QUESTIONS, PLEASE CONTACT MARK SPENCER, TELEPHONE: 571-272-2510; FAX: 571-273-0221

TO REDUCE ERRORED SEQUENCE LISTINGS, PLEASE USE THE **CHECKER VERSION 4.4.0 PROGRAM**, ACCESSIBLE THROUGH THE U.S. PATENT AND TRADEMARK OFFICE WEBSITE. SEE BELOW FOR ADDRESS:

<http://www.uspto.gov/web/offices/pac/checker/chkrnote.htm>

Applicants submitting genetic sequence information electronically on diskette or CD-Rom should be aware that there is a possibility that the disk/CD-Rom may have been affected by treatment given to all incoming mail.

Please consider using alternate methods of submission for the disk/CD-Rom or replacement disk/CD-Rom.

Any reply including a sequence listing in electronic form should NOT be sent to the 20231 zip code address for the United States Patent and Trademark Office, and instead should be sent via the following to the indicated addresses:

1. EFS-Bio (<<http://www.uspto.gov/ebc/efs/downloads/documents.htm>> , EFS Submission User Manual - ePAVE)
2. U.S. Postal Service: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
3. Hand Carry, Federal Express, United Parcel Service, or other delivery service (EFFECTIVE 01/14/05):
U.S. Patent and Trademark Office, Mail Stop Sequence, Customer Window, Randolph Building, 401 Dulany Street, Alexandria, VA 22314

Revised 01/10/06



IFW16

RAW SEQUENCE LISTING

DATE: 06/14/2006

PATENT APPLICATION: US/10/632,645A

TIME: 09:53:30

Input Set : F:\1011CON1.2.ST25.txt

Output Set: N:\CRF4\06142006\J632645A.raw

3 <110> APPLICANT: Coutu, Linda B.

4 Colosi, Peter B.

5 Qian, Xiabong

7 <120> TITLE OF INVENTION: ADENO-ASSOCIATED VECTOR COMPOSITIONS FOR EXPRESSION OF

FACTOR

8 VIII

10 <130> FILE REFERENCE: 1011CON1.2

12 <140> CURRENT APPLICATION NUMBER: US 10/632,645A

13 <141> CURRENT FILING DATE: 2003-08-01

15 <150> PRIOR APPLICATION NUMBER: US 09/740,211

16 <151> PRIOR FILING DATE: 2000-12-18

18 <150> PRIOR APPLICATION NUMBER: US 09/470,618

19 <151> PRIOR FILING DATE: 1999-12-22

21 <150> PRIOR APPLICATION NUMBER: US 09/634,862

22 <151> PRIOR FILING DATE: 1999-07-30

24 <150> PRIOR APPLICATION NUMBER: US 60/125,974

25 <151> PRIOR FILING DATE: 1999-03-24

27 <150> PRIOR APPLICATION NUMBER: US 60/104,994

28 <151> PRIOR FILING DATE: 1998-10-20

30 <160> NUMBER OF SEQ ID NOS: 17

32 <170> SOFTWARE: PatentIn version 3.3

34 <210> SEQ ID NO: 1

35 <211> LENGTH: 59

36 <212> TYPE: DNA

37 <213> ORGANISM: Artificial Sequence

39 <220> FEATURE:

40 <223> OTHER INFORMATION: Oligonucleotide Z8A

42 <400> SEQUENCE: 1

43 cccaagcttg cggccgcccc ggtgccgccc ctaggcaggt aagtgccgtg tgtggttcc 59

46 <210> SEQ ID NO: 2

47 <211> LENGTH: 59

48 <212> TYPE: DNA

49 <213> ORGANISM: Artificial Sequence

51 <220> FEATURE:

52 <223> OTHER INFORMATION: Oligonucleotide Z8A

54 <400> SEQUENCE: 2

55 ccgctcgagc agagctctat ttgcatggtg gaatcgatgc cgcgggaacc acacacggc 59

58 <210> SEQ ID NO: 3

59 <211> LENGTH: 103

60 <212> TYPE: DNA

61 <213> ORGANISM: Artificial Sequence

63 <220> FEATURE:

64 <223> OTHER INFORMATION: PCR fragment Z8

66 <400> SEQUENCE: 3

3,6
Does Not Comply
Corrected Diskette Needed

RAW SEQUENCE LISTING

DATE: 06/14/2006

PATENT APPLICATION: US/10/632,645A

TIME: 09:53:30

Input Set : F:\1011CON1.2.ST25.txt

Output Set: N:\CRF4\06142006\J632645A.raw

```

67 cccaagcttg cgccgcgccg ggtgccgcc ctaggcaggt aagtgccgtg tgtggttccc      60
69 gcggcatcga ttccaccatg caaatagagc tctgctcgag cgg                      103
72 <210> SEQ ID NO: 4
73 <211> LENGTH: 57
74 <212> TYPE: DNA
75 <213> ORGANISM: Artificial Sequence
77 <220> FEATURE:
78 <223> OTHER INFORMATION: Oligonucleotide INT3S
80 <400> SEQUENCE: 4
81 ttcccgcggg cctggcctct ttacgggta tggcccttgc gtgccttgaa ttactga      57
84 <210> SEQ ID NO: 5
85 <211> LENGTH: 57
86 <212> TYPE: DNA
87 <213> ORGANISM: Artificial Sequence
89 <220> FEATURE:
90 <223> OTHER INFORMATION: Oligonucleotide INT3A
92 <400> SEQUENCE: 5
93 gaatcgatac ctgtggagaa aaagaaaaag tggatgtcag tgtcagtaat tcaaggc      57
96 <210> SEQ ID NO: 6
97 <211> LENGTH: 99
98 <212> TYPE: DNA
99 <213> ORGANISM: Artificial Sequence
101 <220> FEATURE:
102 <223> OTHER INFORMATION: PCR fragment INT3
104 <400> SEQUENCE: 6
105 ttcccgcggg cctggcctct ttacgggta tggcccttgc gtgccttgaa ttactgacac    60
107 tgacatccac tttttctttt tctccacagg tatcgattc                          99
110 <210> SEQ ID NO: 7
111 <211> LENGTH: 100
112 <212> TYPE: DNA
113 <213> ORGANISM: Artificial Sequence
115 <220> FEATURE:
116 <223> OTHER INFORMATION: Oligonucleotide EG3S
118 <400> SEQUENCE: 7
119 agggaatggt tgttcttaaa taccatccag ggaatgtttg ttcttaata ccatccaggg    60
121 aatgtttggt cttaaatacc atctacagtt attggttaaa                        100
124 <210> SEQ ID NO: 8
125 <211> LENGTH: 59
126 <212> TYPE: DNA
127 <213> ORGANISM: Artificial Sequence
129 <220> FEATURE:
130 <223> OTHER INFORMATION: Oligonucleotide EG3A
132 <400> SEQUENCE: 8
133 ggaaagggtga tctgtgtgca gaaagactcg ctctaataa cttctttaac caataactg    59
136 <210> SEQ ID NO: 9
137 <211> LENGTH: 144
138 <212> TYPE: DNA
139 <213> ORGANISM: Artificial Sequence
141 <220> FEATURE:

```

RAW SEQUENCE LISTING

DATE: 06/14/2006

PATENT APPLICATION: US/10/632,645A

TIME: 09:53:30

Input Set : F:\1011CON1.2.ST25.txt

Output Set: N:\CRF4\06142006\J632645A.raw

142 <223> OTHER INFORMATION: PCR fragment EG3
 144 <400> SEQUENCE: 9
 145 agggaatggt tgtttcttaaa taccatccag ggaatgtttg ttcttaaata ccatccagg 60
 147 aatgtttgtt cttaaatacc atctacagtt attggttaaa gaagtatt agagcgagtc 120
 149 tttctgcaca cagatcacct ttcc 144
 152 <210> SEQ ID NO: 10
 153 <211> LENGTH: 59
 154 <212> TYPE: DNA
 155 <213> ORGANISM: Artificial Sequence
 157 <220> FEATURE:
 158 <223> OTHER INFORMATION: Oligonucleotide SPA.S
 160 <400> SEQUENCE: 10
 161 tcgagaataa aagatcagag ctctagagat ctgtgtgttg gttttttgtg tgcggccgc 59
 164 <210> SEQ ID NO: 11
 165 <211> LENGTH: 59
 166 <212> TYPE: DNA
 C--> 167 <213> ORGANISM: Artificial Sequence
 W--> 169 <220> FEATURE:
 W--> 169 <223> OTHER INFORMATION: see p. 6 for even explanation
 W--> 169 <400> 11
 170 tcgagcgcc gcacacaaaa aaccaacaca cagatctcta gagctctgat cttttattc 59
 173 <210> SEQ ID NO: 12
 174 <211> LENGTH: 63
 175 <212> TYPE: DNA
 176 <213> ORGANISM: Artificial Sequence
 178 <220> FEATURE:
 179 <223> OTHER INFORMATION: PCR fragment SPA
 181 <400> SEQUENCE: 12
 182 tcgagaataa aagatcagag ctctagagat ctgtgtgttg gttttttgtg tgcggccgct 60
 184 cga 63
 187 <210> SEQ ID NO: 13
 188 <211> LENGTH: 11933
 189 <212> TYPE: DNA
 190 <213> ORGANISM: Artificial Sequence
 192 <220> FEATURE:
 193 <223> OTHER INFORMATION: Vector from ITR to ITR
 195 <400> SEQUENCE: 13
 196 cagctgcgcg ctgcctcgt cactgaggcc gcccgggcaa agcccgggcg tggggcgacc 60
 198 tttggtcgcc cggcctcagt gagcgagcga gcgcgcagag agggagtggc caactccatc 120
 200 actaggggtt cctgcggccg ccaggggaat gttgttctt aaataccatc caggggaatgt 180
 202 ttgttcttaa ataccatcca ggggaatgtt gttcttaaat accatctaca gttattggtt 240
 204 aaagaagtat attagagcga gtctttctgc acacagatca cctttccggg tgcgcgccct 300
 206 aggcaggtaa gtgcctgtg tggttcccgc gggcctggcc tctttacggg ttatggccct 360
 208 tgcgtgcctt gaattactga cactgacatc cactttttct tttctccac aggtatcgat 420
 210 tccaccatgc aaatagagct ctccacctgc ttctttctgt gccttttgcg attctgcttt 480
 212 agtgccacca gaagatacta cctgggtgca gtggaactgt catgggacta tatgcaaagt 540
 214 gatctcggtg agctgcctgt ggacgcaaga ttctctcta gagtgccaaa atcttttcca 600
 216 ttcaaacct cagctgtgta caaaaagact ctgtttgtag aattcacgga tcaccttttc 660
 218 aacatcgcta agccaaggcc accctggatg ggtctgctag gtctaccat ccaggctgag 720

RAW SEQUENCE LISTING

PATENT APPLICATION: US/10/632,645A

DATE: 06/14/2006

TIME: 09:53:30

Input Set : F:\1011CON1.2.ST25.txt

Output Set: N:\CRF4\06142006\J632645A.raw

220	gtttatgata	cagtggcat	tacacttaag	aacatggctt	cccatcctgt	cagtcttcat	780
222	gctgttggtg	tatcctactg	gaaagcttct	gagggagctg	aatatgatga	tcagaccagt	840
224	caaagggaga	agaagatga	taaagtcttc	cctgggtggaa	gccatacata	tgtctggcag	900
226	gtcctgaaag	agaatgggtcc	aatggcctct	gacccactgt	gccttaccta	ctcatatctt	960
228	tctcatgttg	acctggtaaa	agacttgaat	tcaggcctca	ttggagccct	actagtatgt	1020
230	agagaaggga	gtctggccaa	ggaaaagaca	cagaccttgc	acaaatttat	actacttttt	1080
232	gctgtatttg	atgaaggga	aagttggcac	tcagaaacaa	agaactcctt	gatgcaggat	1140
234	agggatgctg	catctgctcg	ggcctggcct	aaaatgcaca	cagtcaatgg	ttatgtaaac	1200
236	aggtctctgc	caggtctgat	tggatgccac	aggaaatcag	tctattggca	tgtgattgga	1260
238	atgggcacca	ctcctgaagt	gcaactcaata	ttcctcgaag	gtcacacatt	tcttgtgagg	1320
240	aaccatcgcc	aggcgtcctt	ggaaatctcg	ccaataactt	tccttactgc	tcaaacactc	1380
242	ttgatggacc	ttggacagtt	tctactgttt	tgtcatatct	cttccacca	acatgatggc	1440
244	atggaagctt	atgtcaaat	agacagctgt	ccagaggaa	cccaactacg	aatgaaaaat	1500
246	aatgaagaag	cgaagacta	tgatgatgat	cttactgatt	ctgaaatgga	tgtggtcagg	1560
248	tttgatgatg	acaactctcc	ttcctttatc	caaattcgct	cagttgccaa	gaagcctcct	1620
250	aaaacttggg	tacattacat	tgctgctgaa	gaggaggact	gggactatgc	tcctttagtc	1680
252	ctcgcccccg	atgacagaag	ttataaaaagt	caatatttga	acaatggccc	tcagcggatt	1740
254	ggtaggaagt	acaaaaaagt	ccgatttatg	gcatacacag	atgaaacctt	taagactcgt	1800
256	gaagctattc	agcatgaatc	aggaatcttg	ggacctttac	tttatgggga	agttggagac	1860
258	acactgttga	ttatattta	gaatcaagca	agcagaccat	ataacatcta	ccctcacgga	1920
260	atcactgatg	tcgctccttt	gtattcaagg	agattacca	aaggtgtaaa	acatttgaag	1980
262	gattttccaa	ttctgccagg	agaaatatcc	aaatataaat	ggacagtgc	tgtagaagat	2040
264	gggccaacta	aatcagatcc	tcggtgcctg	accgcctatt	actctagtgt	cgtaaataatg	2100
266	gagagagatc	tagcttcagg	actcattggc	cctctcctca	tctgctacaa	agaatctgta	2160
268	gatcaaaag	gaaaccagat	aatgtcagac	aagagggaatg	tcacctctgt	ttctgtatgt	2220
270	gatgagaacc	gaagctggta	cctcacagag	aatatacaac	gctttctccc	caatccagct	2280
272	ggagtgcagc	ttgaggatcc	agagttccaa	gcctccaaca	tcatgcacag	catcaatggc	2340
274	tatgtttttg	atagtttgca	gttgctcagtt	tgtttgcatg	aggtggcata	ctggtacatt	2400
276	ctaagcattg	gagcacagac	tgacttcctt	tctgtcttct	tctctggata	taccttcaaa	2460
278	cacaaaatgg	tctatgaaga	cacactcacc	ctattcccat	tctcaggaga	aactgtcttc	2520
280	atgtcgatgg	aaaaccagg	tctatggatt	ctgggggtgc	acaactcaga	ctttcggaac	2580
282	agaggcatga	ccgccttact	gaagggttct	agttgtgaca	agaactctgg	tgattattac	2640
284	gaggacagtt	atgaagatat	ttcagcatat	ttgctgagta	aaaacaatgc	cattgaacca	2700
286	agaagcttcg	aaataactcg	tactactctt	cagtcagatc	aagaggaaat	tgactatgat	2760
288	gataccatat	cagttgaaat	gaagaaggaa	gattttgaca	tttatgatga	ggatgaaaat	2820
290	cagagccccc	gcagctttca	aaagaaaaca	cgacactatt	ttattgctgc	agtgagagg	2880
292	ctctgggatt	atgggatgag	tagctcccca	catgttctaa	gaaacagggc	tcagagtggc	2940
294	agtgtccctc	agttcaagaa	agttgttttc	caggaattta	ctgatggctc	ctttactcag	3000
296	cccttatacc	gtggagaact	aaatgaacat	ttgggactcc	tggggccata	tataagagca	3060
298	gaagtgaag	ataatatcat	ggtaactttc	agaaatcagg	cctctcgtcc	ctattccttc	3120
300	tattctagcc	ttatttctta	tgaggaagat	cagaggcaag	gagcagaacc	tagaaaaaac	3180
302	tttgtaagc	ctaatgaaac	caaaacttac	ttttggaaag	tgcaacatca	tatggcacc	3240
304	actaaagatg	agtttgactg	caaagcctgg	gcttatttct	ctgatgttga	cctggaaaaa	3300
306	gatgtgcact	caggcctgat	tggacccctt	ctggtctgcc	acactaacac	actgaaccct	3360
308	gctcatggga	gacaagtgc	agtacaggaa	tttgcctctg	ttttcaccat	ctttgatgag	3420
310	accaaagct	ggtacttcac	tgaaaactatg	gaaagaaact	gcagggtctc	ctgcaatatc	3480
312	cagatggaag	atcccacttt	taaagagaat	tatcgcttcc	atgcaatcaa	tggctacata	3540
314	atggatacac	tacctggctt	agtaatggct	caggatcaaa	ggattcgatg	gtatctgctc	3600
316	agcatgggca	gcaatgaaaa	catccattct	attcatttca	gtggacatgt	gttccactgta	3660

RAW SEQUENCE LISTING

DATE: 06/14/2006

PATENT APPLICATION: US/10/632,645A

TIME: 09:53:30

Input Set : F:\1011CON1.2.ST25.txt

Output Set: N:\CRF4\06142006\J632645A.raw

318	cgaaaaaaag	aggagtataa	aatggcactg	tacaatctct	atccaggtgt	ttttgagaca	3720
320	gtggaaatgt	taccatccaa	agctggaatt	tggcggtgg	aatgccttat	tggcgagcat	3780
322	ctacatgctg	ggatgagcac	actttttctg	gtgtacagca	ataagtgtca	gactcccctg	3840
324	ggaatggctt	ctggacacat	tagagatttt	cagattacag	cttcaggaca	atatggacag	3900
326	tgggccccaa	agctggccag	acttcattat	tccggatcaa	tcaatgcctg	gagcaccaag	3960
328	gagccctttt	cttggatcaa	ggtggatctg	ttggcaccaa	tgattattca	cggcatcaag	4020
330	acccaggggtg	cccgtcagaa	gttctccagc	ctctacatct	ctcagtttat	catcatgtat	4080
332	agtcttgatg	ggaagaatg	gcagacttat	cgaggaaatt	ccactggaac	cttaatggtc	4140
334	ttctttggca	atgtggattc	atctgggata	aaacacaata	tttttaaccc	tccaattatt	4200
336	gctcgataca	tccgtttgca	cccaactcat	tatagcattc	gcagcactct	tgcgatggag	4260
338	ttgatggggt	gtgatttaaa	tagttgcagc	atgccattgg	gaatggagag	taaagcaata	4320
340	tcagatgcac	agattactgc	ttcatcctac	tttaccataa	tgtttgccac	ctgggtctct	4380
342	tcaaaagctc	gacttcacct	ccaagggagg	agtaatgcct	ggagacctca	ggtgaataat	4440
344	ccaaaagagt	ggctgcaagt	ggacttccag	aagacaatga	aagtcacagg	agtaactact	4500
346	cagggagtaa	aatctctgct	taccagcatg	tatgtgaagg	agttcctcat	ctccagcagt	4560
348	caagatggcc	atcagtggac	tctctttttt	cagaatggca	aagtaaaggt	ttttcaggga	4620
350	aatcaagact	ccttcacacc	tgtggtgaac	tctctagacc	caccgttact	gactcgctac	4680
352	cttcgaattc	acccccagag	ttgggtgcac	cagattgccc	tgaggatgga	ggttctgggc	4740
354	tgcgaggcac	aggacctcta	ctgactcgag	aataaaaagat	cagagctcta	gagatctgtg	4800
356	tgttggtttt	ttgtgtgcgg	ccgcaggaac	ccctagtgat	ggagtgggcc	actccctctc	4860
358	tgcgcgctcg	ctcgctcact	gagggccgggc	gaccaaagggt	cgcccgacgc	ccgggctttg	4920
360	cccgggcggc	ctcagtgagc	gagcgagcgc	gcagctgcct	gcaggacatg	tgagcaaaaag	4980
362	ggccgcaaaa	ggccaggaac	cgtaaaaagg	ccgcgttgct	ggcggttttc	cataggctcc	5040
364	gccccctga	cgagcatcac	aaaaatcgac	gctcaagtca	gaggtggcga	aaaccgacag	5100
366	gactataaag	ataccaggcg	tttccccctg	gaagctccct	cgtgcgctct	cctgttccga	5160
368	ccctgccgct	taccggatac	ctgtccgcct	ttctcccttc	gggaagcgtg	gcgctttctc	5220
370	atagctcacg	ctgtaggtat	ctcagttcgg	tgtaggtcgt	tcgctccaag	ctgggctgtg	5280
372	tgcacgaacc	ccccgttcag	cccgaccgct	gcgccttacc	cggttaactat	cgtcttgagt	5340
374	ccaaccgggt	aagacacgac	ttatcgccac	tggcagcagc	cactggtaac	aggattagca	5400
376	gagcgaggta	tgtaggcggt	gctacagagt	tcttgaagtg	gtggcctaac	tacggctaca	5460
378	ctagaaggac	agtatttgggt	atctgcgctc	tgctgaagcc	agttaccttc	ggaaaaagag	5520
380	ttggtagctc	ttgatccggc	aaacaaacca	ccgctggtag	cggtggtttt	tttgtttgca	5580
382	agcagcagat	tacgcgcaga	aaaaaaggat	ctcaagaaga	tcctttgatc	ttttctacgg	5640
384	ggtctgacgc	tcagtgaac	gaaaactcac	gttaagggat	tttggtcatg	agattatcaa	5700
386	aaaggatctt	cacctagatc	cttttaaat	aaaaatgaag	ttttaaatca	atctaaagta	5760
388	tatatgagta	aacttggtct	gacagttacc	aatgcttaat	cagtgaggca	cctatctcag	5820
390	cgatctgtct	atttcgttca	tccatagttg	cctgactccc	cgctcgttag	ataactacga	5880
392	tacgggaggg	cttaccatct	ggccccagtg	ctgcaatgat	accgcgagac	ccacgctcac	5940
394	cggctccaga	tttatcagca	ataaaccagc	cagccggaag	ggccgagcgc	agaagtggtc	6000
396	ctgcaacttt	atccgcctcc	atccagtcta	ttaatgtttg	ccgggaagct	agagtaagta	6060
398	gttcgccagt	taatagtttg	cgcaacgttg	ttgccattgc	tacaggcatc	gtggtgtcac	6120
400	gctcgtcggt	tggtatggct	tcattcagct	ccggttccca	acgatcaagg	cgagttacat	6180
402	gatcccccat	gttgtgcaaa	aaagcgggta	gctccttcgg	tcctccgatc	gttgtcagaa	6240
404	gtaagtggc	cgcagtgtta	tcactcatgg	ttatggcagc	actgcataat	tctcttactg	6300
406	tcatgccatc	cgtaagatgc	ttttctgtga	ctggtgagta	ctcaaccaag	tcattctgag	6360
408	aatagtgtat	gcggcgaccg	agttgctctt	gcccggcgctc	aatacgggat	aataccgcgc	6420
410	cacatagcag	aactttaaaa	gtgctcatca	ttggaaaacg	ttcttcgggg	cgaaaactct	6480
412	caaggatctt	accgctgttg	agatccagtt	cgatgtaacc	cactcgtgca	cccaactgat	6540
414	cttcagcatc	ttttactttc	accagcgttt	ctgggtgagc	aaaaacagga	aggcaaaatg	6600

RAW SEQUENCE LISTING ERROR SUMMARY
PATENT APPLICATION: US/10/632,645A

DATE: 06/14/2006
TIME: 09:53:31

Input Set : F:\1011CON1.2.ST25.txt

Output Set: N:\CRF4\06142006\J632645A.raw

error explanation
Use of <220> Feature (NEW RULES):

Sequence(s) are missing the <220> Feature and associated headings.

Use of <220> to <223> is MANDATORY if <213> ORGANISM is "Artificial Sequence" or "Unknown". Please explain source of genetic material in <220> to <223> section (See "Federal Register," 6/01/98, Vol. 63, No. 104, pp.29631-32) (Sec.1.823 of new Rules)

Seq#:11

VERIFICATION SUMMARY

PATENT APPLICATION: US/10/632,645A

DATE: 06/14/2006

TIME: 09:53:31

Input Set : F:\1011CON1.2.ST25.txt

Output Set: N:\CRF4\06142006\J632645A.raw

L:167 M:220 C: Keyword misspelled or invalid format, <213> ORGANISM for SEQ ID#:11
L:169 M:258 W: Mandatory Feature missing, <220> Tag not found for SEQ#:11, <213>
ORGANISM:Artificial Sequence
L:169 M:258 W: Mandatory Feature missing, <223> Tag not found for SEQ#:11, <213>
ORGANISM:Artificial Sequence
L:169 M:258 W: Mandatory Feature missing, <223> Blank for SEQ#:11,Line#:169